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Review

From Cradle to Grave: The Multiple Roles of Fibroblast Growth Factors in Neural Development

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The generation of a functional nervous system involves a multitude of steps that are controlled by just a few families of extracellular signaling molecules. Among these, the fibroblast growth factor (FGF) family is particularly prominent for the remarkable diversity of its functions. FGFs are best known for their roles in the early steps of patterning of the neural primordium and proliferation of neural progenitors. However, other equally important functions have emerged more recently, including in the later steps of neuronal migration, axon navigation, and synaptogenesis. We review here these diverse functions and discuss the mechanisms that account for this unusual range of activities. FGFs are essential components of most protocols devised to generate therapeutically important neuronal populations in vitro or to stimulate neuronal repair in vivo. How FGFs promote the development of the nervous system and maintain its integrity will thus remain an important focus of research in the future.

Introduction

The vertebrate nervous system is without doubt the most complex organ of the living world, in both morphological organization and cellular diversity. Understanding how this complexity is generated is a topic of obvious interest to developmental biologists, and for neuroscientists it is an important source of insights into the logic of the organization and function of the adult brain. Of the many molecules that are implicated in neural development, fibroblast growth factors (FGFs) may have the most widespread and best-documented roles in generating the cellular diversity and morphological complexity of the nervous system. New functions of FGFs have recently been discovered and progress has also been made in understanding the modes of propagation and action of these molecules. The time is therefore ripe to review these recent developments alongside better-known functions of FGFs in neural development.

The first part of this review will examine succinctly the diverse components of FGF signaling pathways. For more detailed information, the reader is directed to several excellent reviews on this topic (Böttcher and Niehrs, 2005; Mason, 2007). The next two sections will discuss the remarkable range of functions that FGFs serve in proliferating progenitors and in differentiating neurons, respectively. The fourth section will then consider the multiple connections of FGFs with disease, including the direct implication of particular FGFs in human pathologies and the use of FGFs to generate cells of potential therapeutic use. Because of the vastness of the subject and the limited space available, we will not attempt to be comprehensive. Our aim is to outline the most significant activities exerted by FGFs in the developing nervous system, focusing on vertebrates, and to identify common threads and unique features among them.

Molecular Features of FGF Signaling

FGFs and Their Receptors

The first known FGF ligands, FGF1 and FGF2, were purified in 1975 from the brain and pituitary on the basis of their ability to stimulate the proliferation of mouse fibroblasts. Other FGFs were then identified as oncogenes or growth factors for other cell types, and additional family members were later discovered by their conserved sequences. Sequencing of the human and mouse genomes revealed a total of 22 Fgf genes in each species. Fewer Fgfs exist in invertebrates, with two genes in *C. elegans* (egl-17 and let-756) and three in *Drosophila* (branchless, pyramus, and thisbe).

Phylogenic and gene location analysis indicate that the human and mouse FGF families comprise seven subfamilies whose members share synteny, greater homology, and similar binding specificities to receptors (Itoh and Ornitz, 2008; Figure 1). Most FGF family members are classical signaling molecules that are secreted in the extracellular space, where they bind to heparan sulfate proteoglycans (HSPGs). They act in an autocrine or paracrine fashion by interacting with high affinity and different degrees of specificity, with tyrosine kinase receptors present at the cell surface. However, a subset of FGFs called "hormone-like" FGFs (including FGF15/19, FGF21, and FGF23) have reduced heparan-binding affinity and act at a long distance as endocrine factors to regulate metabolism. A third subset of FGFs, called intracellular FGFs (including FGF11 to 14), are not secreted and do not activate FGF receptors but localize to the nucleus or interact with the intracellular domains of voltage-gated sodium channels (Itoh and Ornitz, 2008). This review will focus on the canonical and nuclear FGFs, since they include all the factors that have been implicated in neural development.

The receptors of the FGFs (FGFRs) form a subfamily of cell surface receptor tyrosine kinases (RTKs) that includes four

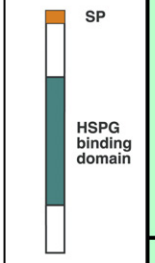
LIGANDS				RECEPTORS		
Scheme	Family		Members	FGFR	Isoforms	Scheme
	cFGFs	FGF4	FGF3	*1, 2*	IIIb	
			FGF4	1, 2, *3*, 4	IIIc	
			FGF6	*1, 2,* 4		
		FGF5	FGF1	1, 2, 3, 4	IIIb, IIIc	
			FGF2	1, 2, 3, 4		
			FGF5	*1, 2*	IIIc	
		FGF8	FGF8	*1*, 2, **3, 4**	IIIc	
			FGF17	*1*, 2, 3, *4*		
			FGF18	*2, 3, 4*		
		FGF9	FGF9	*2*, 3	IIIb, IIIc	
			FGF16	*2, 3*	IIIc	
			FGF20	*1, 2,* 3, *4*	IIIb, IIIc	
		FGF10	FGF7	**2, 4**	IIIb	
			FGF10	*1, 2*		
			FGF22	*1, 2*		
	hFGFs	FGF15/19	FGF15/19	1, **2, 3, 4**	IIIb, IIIc	
			FGF21	*1, 2, 3, 4*		
			FGF23	*1, 2, 3,* **4**		
	iFGFs	FGF11	FGF11			
			FGF12			
			FGF13			
			FGF14			

Figure 1. Structure and Phylogeny of FGF Ligands and Specificity of Their Interactions with FGF Receptors

The 22 human and mouse FGF ligands can be subdivided in canonical (cFGFs), intracellular (iFGFs), and hormone-like (hFGFs) subfamilies (Itoh and Ornitz, 2008). All FGFs present a heparan sulfate proteoglycan (HSPG) binding domain and most have a N-terminal signal peptide (SP) and are secreted via a classical secretory pathway. The three members of the FGF9 subfamily (FGF9, 16, and 20) are efficiently secreted but have uncleavable signal sequences, while the two FGF1 subfamily members (FGF1 and FGF2) lack identifiable signal sequences and are secreted by noncanonical pathways. The four FGF11-related factors (FGF11 to 14) are not secreted and do not activate FGF receptors but localize to the nucleus (Itoh and Ornitz, 2008).

The family of FGF receptors contains four main members (FGFR1 to 4). Their extracellular domain is composed of three Immunoglobulin-like domains (IgGI-IgGIII) involved in FGF ligand binding, an acid box (AB) domain, and a HSPG-binding region, which are involved in interaction of the receptors with extracellular molecules, particularly HSPGs, and with cell adhesion molecules (CAMs). Following the transmembrane domain (TM), the intracellular domain harbors a classical split tyrosine kinase domain (KI, KII), which contains the catalytic activity of the receptor as well as autophosphorylation sites that interact with intracellular substrates (see Figure 2). Tissue-specific alternative splicing events encompassing half of IgGIII generate two isoforms, IIIb and IIIc, which have very different ligand binding specificities (Zhang et al., 2006). FGFR numbers depicted in bold letters indicate high-affinity binding to the ligand in the same line; in plain letters they indicate intermediate affinity binding, and in italic they indicate lower affinity binding.

receptors in vertebrates (FGFR1 to 4), two in *Drosophila* (heartless and breathless), and one in *C. elegans* (egl-15). They are single spanning transmembrane proteins, with an extracellular domain that binds to FGF ligands, heparan sulfate proteoglycans, and cell adhesion molecules, and an intracellular domain that harbours the tyrosine kinase activity of the receptor and interacts with intracellular substrates and signal transduction molecules (Böttcher and Niehrs, 2005) (Figure 1). FGFRs exist in multiple isoforms, in particular isoforms b and c that are generated by tissue-specific alternative splicing events and have very different FGF-binding specificities (Zhang et al., 2006; Figure 1). However, the specificities of FGF ligand-receptor interactions have been established in a cell culture assay, and since these interactions are strongly influenced by cofactors such as HSPGs, they may differ substantially in an in vivo context.

Signal Transduction Pathways Downstream of FGFRs

Binding of FGFs to FGFRs triggers receptor dimerization and tyrosine kinase activation, resulting in autophosphorylation of the intracellular domain of the receptor and recruitment and assembly of signaling complexes. Multiple pathways have been shown to operate downstream of FGFRs (Figure 2). Briefly, the MAPK/Erk signaling cascade is the pathway most commonly employed by FGFRs and results in stimulation of the expression and/or activation of various transcription factors that act as effectors of the pathway, including Ets proteins, AP1, GATA proteins, c-*myc*, and CREB (Yordy and Muise-Helmericks, 2000), and in the induction of multiple feedback inhibitors including Sef, MKP3, and Sproutys (Figure 2; see below). The MAPK/Erk pathway is particularly important in mediating the proliferative activity of FGFs. Activation of a second pathway, the PLCγ/Ca^{2+} pathway, has been implicated in the stimulation of neurite outgrowth by FGF2 (Doherty and Walsh, 1996). The PI3 kinase/Akt pathway mediates some of the activities of FGFs in other tissues but there is little evidence for its role in neural development in vivo downstream of FGFRs. An additional transduction pathway involving the docking proteins FRS2 α and β and the small GTPases Rnd1 and RhoA has been shown to mediate the effect of FGF signaling on cytoskeletal rearrangements and neurite outgrowth in PC12 cells (Harada et al., 2005).

Feedback Loops and Other Regulatory Mechanisms

FGF signaling is regulated at multiple levels, resulting in a tight control of its level, its spread, and its timing. Some of the mechanisms involved are specific to FGF signaling while others regulate RTK signaling in general. Interaction of FGFs and their receptors with heparan sulfate proteoglycans (HSPGs) in the extracellular space is central to FGF signaling, as HSPGs are required both for high-affinity binding of FGFs to their receptors and for the bridging of the two subunits of FGFR dimers that is required for their autophosphorylation (Figure 3). Moreover, HSPGs contribute to the specificity of the interaction between FGF-FGFR pairs, protect FGFs from degradation, and limit their diffusion. They represent a highly diverse group of molecules with complex temporal and spatial expression patterns and there is accumulating experimental evidence of their importance in FGF signaling at different stages of neural development (Grobe et al., 2005; Jen et al., 2009; Sirko et al., 2010; see Figure 3).

Many of the molecules regulating FGF signaling are themselves regulated by FGFs in positive or negative feedback loops. The transmembrane protein Sef and the intracellular proteins Sprouty, which inhibit MAPK signaling downstream of FGFRs by interacting with different components of the pathway, are part of the Fgf8 synexpression group (i.e., their expression patterns in embryos are similar to that of Fgf8 as a result of their

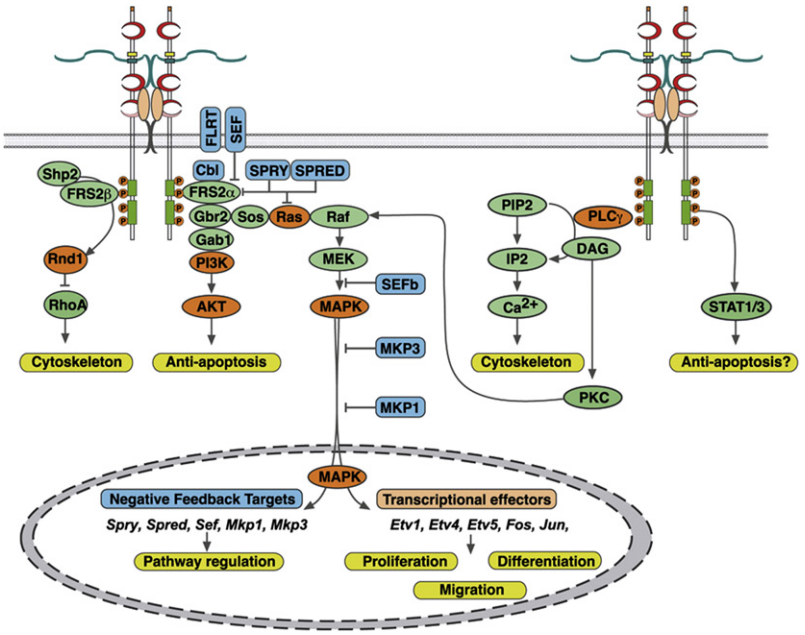


Figure 2. Intracellular Signaling Pathways Activated Downstream of FGF Receptors

The four pathways operating downstream of activated FGFRs that are mentioned in the text are illustrated in the figure. The Ras/MAPK/Erk pathway involves the lipid-anchored docking protein FRS2, which is constitutively bound to FGFR1 and becomes phosphorylated upon FGFR activation. Phosphorylated FRS2 is bound by the adaptor protein Grb2, resulting in formation of a multi-protein complex that localizes to the cell membrane and activates the Ras-MAPK signaling cascade. This cascade results in transcriptional activation and/or stabilization of feedback inhibitors and transcriptional effectors of the pathway. The PI3 kinase/Akt pathway can be activated by several mechanisms downstream of FGFRs, including the recruitment of Gab1 by Grb2. Activation of the PLCγ/Ca^{2+} pathway is initiated by recruitment of PLCγ to a phosphorylated tyrosine of FGFR1. Green cartouches indicate the main components of the pathways; orange cartouches, the components that give their names to the pathways; blue cartouches, the regulators; and yellow cartouches, the cellular functions of the pathways.

induction by FGF signaling). Not surprisingly given the importance of FGF signaling in brain development, the fine-tuning of the pathway by Sprouty and Sef is essential for proper brain morphogenesis (Faedo et al., 2010; Labalette et al., 2011).

Generation of Neural Stem Cells

Neural Induction

The development of the nervous system in vertebrates begins with the acquisition of a neural fate by the dorsal ectoderm of the gastrulating embryo, a process known as neural induction. An early ''default model'' of neural induction postulated that induction of neural tissue in *Xenopus* embryos only requires inhibition of bone morphogenetic protein (BMP) signaling, which counters the intrinsic tendency of ectoderm to adopt a neural fate. However, it is now clear that FGF signaling also has a crucial role in neural induction in amphibians, fish, and birds (Delaune et al., 2005; Kudoh et al., 2004; Rentzsch et al., 2004; Stern, 2005). FGFs act in part by antagonizing BMP signaling through phosphorylation and inhibition of the BMP effector Smad1 and direct repression of BMP transcription (Londin et al., 2005; Pera et al., 2003), but they also act independently of BMP, for example by inducing the expression of Zic3, a transcription factor required for neural fate specification in *Xenopus* embryos (Marchal et al., 2009). Experiments involving the grafting of cell pellets or beads releasing growth factors into chick embryos have provided evidence that FGFs act at multiple steps during neural induction in this model, initiating expression of markers of a ''preneural state'' on their own, but acting in combination with Wnt- and BMP-antagonists to induce additional neural markers (Albazerchi and Stern, 2007). In the ascidian sea squirt, FGFs rather than BMP inhibitors are the main inducers of neural cell fates (Bertrand et al., 2003).

Neural Plate Patterning

Neural induction is intimately linked to the subsequent step of neural plate patterning, as cells of the neural plate simultaneously acquire their neural fate and their positional information. FGFs, produced in gastrulating mouse embryos by the node and the primitive streak and later by the posterior neural plate, have been implicated, together with Wnt and retinoic acid (RA), in the specification of posterior neural fates, either directly or by posteriorization of the caudal plate (Bel-Vialar et al., 2002; Kudoh et al., 2004; Rentzsch et al., 2004; Stern, 2005; Takemoto et al., 2006). Exposure of chick embryos or mouse neural plate explants to FGFs at increasing concentrations or for increasing durations induces progressively more posterior fates, marked by the expression of different Hox and Cdx genes, resulting in the specification of motor neuron pools of different anterior-posterior identity (Liu et al., 2001).

FGFs also have a major role in induction and patterning of the peripheral nervous system, which develops from the neural crest in the trunk of the embryo and from both ectodermal placodes and the neural crest in the head (McCabe and Bronner-Fraser, 2009; Streit, 2007). FGFs act at multiple stages, first initiating the formation of a ''border region'' surrounding the neural plate, where different levels of BMP and Wnt signals determine whether cells adopt a neural crest or a placode fate. FGF signals are then required again for the induction of the different placodes; FGF3 and FGF8 induce the otic placode that gives rise to the inner ear and the epibranchial placodes that generate cranial ganglia, while FGF8 induces the olfactory placode, which develops into the olfactory sensory epithelium. The outstanding question of how the same FGF signals induce distinct placodes at different locations is being actively investigated.

Regionalization of the Neural Primordium

After the induction and initial patterning of the neural plate during gastrulation, the positional identities of cells along the antero-posterior axis of the neural plate are refined and maintained by several local organizing centers, which influence the fate, growth, and organization of adjacent tissues in a position-specific manner by emitting secreted signaling molecules. FGF signaling is a common feature of the activity of most neural plate

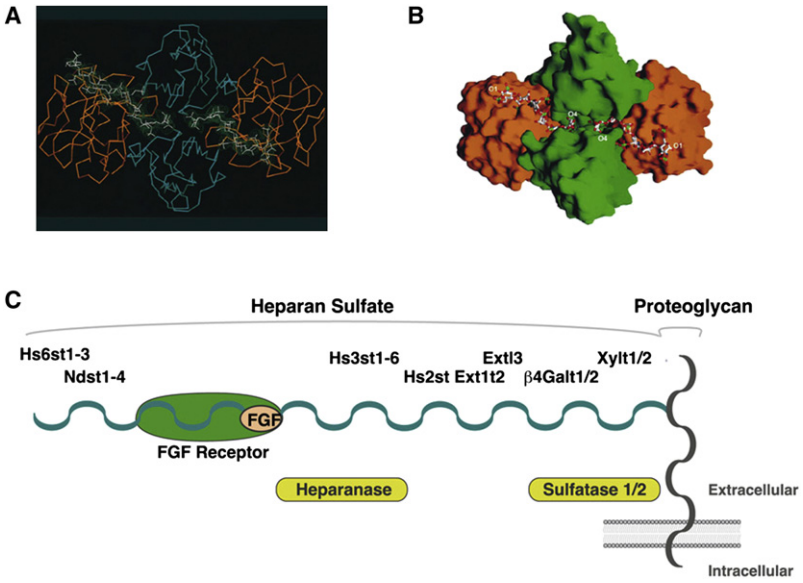


Figure 3. Ternary Complexes Comprising FGFs, FGFRs, and Heparan Sulfate Proteoglycans

(A) Tridimensional structure of a 2:2:2 dimeric ternary complex between FGF2 (orange), FGFR1 (blue), and the heparan sulfate moiety of a heparan sulfate proteoglycan (HSPG) (white). Reproduced from Schlessinger et al. (2000).

(B) Molecular surface representation of the same dimeric ternary complex. Reproduced from Schlessinger et al. (2000).

(C) HSPGs are essential for the assembly of the FGF-FGFR complex, as their negative charges create binding sites for both FGF and FGFR. Regulation of HSPG synthesis can therefore modulate FGF signaling extensively. Twenty-six enzymes are responsible for the assembly of heparan sulfate chains. For example, Ndst1 catalyzes the first sulfation step during heparan sulfate synthesis and *Ndst1* mutant embryos present defects in telencephalic development that are similar to those of Fgf8 mutant embryos (Grobe et al., 2005). Enzymes that cleave heparan sulfate chains (heparanases) or remove the sulfates (sulfatases) have also been shown to modulate FGF signaling.

organizing centers, including the rostral signaling center of the anterior forebrain, the zona limitans intrathalamica in the thalamus, the isthmic organizer at the boundary between the prospective midbrain and hindbrain, and the organizer in rhombomere 4 of the hindbrain (Rhinn et al., 2006; Figure 4). The isthmic organizer produces several FGFs, including two splicing isoforms of FGF8 (FGF8a and FGF8b), FGF17, and FGF18, which collectively orchestrate the development of the midbrain anteriorly and the cerebellum posteriorly. Culture of mouse brain explants with FGF-soaked beads and misexpression of FGFs in the brain of chick embryos have revealed that FGF8a, FGF17, and FGF18 promote midbrain development by activating low to medium levels of FGFR signaling, while FGF8b induces a cerebellar fate by eliciting higher levels of signaling because of its higher affinity toward the c isoform of FGFR3 (Liu et al., 2003; Olsen et al., 2006; Sato et al., 2001; Figure 4A). Once the hindbrain and midbrain have been specified, isthmic FGF ligands become involved in the generation of specific types of neurons in these two brain regions. Treatment of rat explants from different regions of the neural plate with various combinations of growth factors and blocking antibodies showed that FGFs specify noradrenergic and serotoninergic neurons in the hindbrain and dopaminergic neurons in the midbrain, by interacting with signals that pattern the neural tube along the dorso-ventral axis, including BMPs and Sonic Hedgehog (Shh) (Partanen, 2007; Ye et al., 1998).

The sequential involvement of FGF signals in multiple steps of development of the same territory is a recurrent theme in brain development, best exemplified by the development of the forebrain. Fgf8 is initially expressed by the rostral signaling center located at the anterior margin of the neural plate, and it remains expressed in this region as the neural plate folds and fuses to form the telencephalic primordium (Crossley et al., 2001). A detailed analysis of telencephalic development in mice carrying various mutant alleles of Fgf8 or ectopically expressing FGF8 showed that this signal initially confers a telencephalic character to the anterior neural plate, through regulation of the expression and activity of other signaling molecules including Wnts, BMPs, and Shh (Shimogori et al., 2004; Storm et al., 2006; Figure 4C). Deletion of the three Fgfrs expressed in the developing forebrain, Fgfr1-3, showed that FGF signaling also maintains survival of telencephalic progenitors (Paek et al., 2009). In addition to this global role of FGF signaling in telencephalic development, analysis of embryos with reduced or increased levels of Fgf8 expression, or lacking Fgfr1 and 2 but retaining Fgfr3, revealed that FGF signaling also specifies ventral telencephalic fates downstream of Shh signaling (Gutin et al., 2006; Shinya et al., 2001; Storm et al., 2006).

Once the dorsal and ventral subdivisions of the telencephalic vesicles have been established, FGFs remain involved in the subsequent development of these territories and particularly in the subdivision of the dorsal cerebral cortex into multiple functional areas that control sensory perception, motor activity, and behavior in adult organisms. Studies performed in the last decade have established that cortical areas acquire distinct molecular identities around the time of birth and that FGF8 and other FGFs secreted by the rostral signaling center specify anterior cortical areas by regulating the regional expression of multiple transcription factors in the cortical neuroepithelium (Hoch et al., 2009; O'Leary and Sahara, 2008). Overexpression of Fgf8 in the early cortical primordium of mouse embryos results in a massive expansion of anterior cortex without change in overall cortical size and its ectopic expression posteriorly results in duplication of anterior cortical territory, while reducing FGF8 activity results in contraction of anterior cortical areas (Fukuchi-Shimogori and Grove, 2001; Garel et al., 2003). FGF8 patterns the anterior cortex by suppressing in a dose-dependent manner the anterior expression of Emx2 and CoupTF1, two transcription factors specifying posterior area identities. FGF8 also activates several transcription factors anteriorly including Sp8, which maintains the expression of Fgf8 in a positive feedback loop (Cholfin and Rubenstein, 2008; Garel et al., 2003; O'Leary

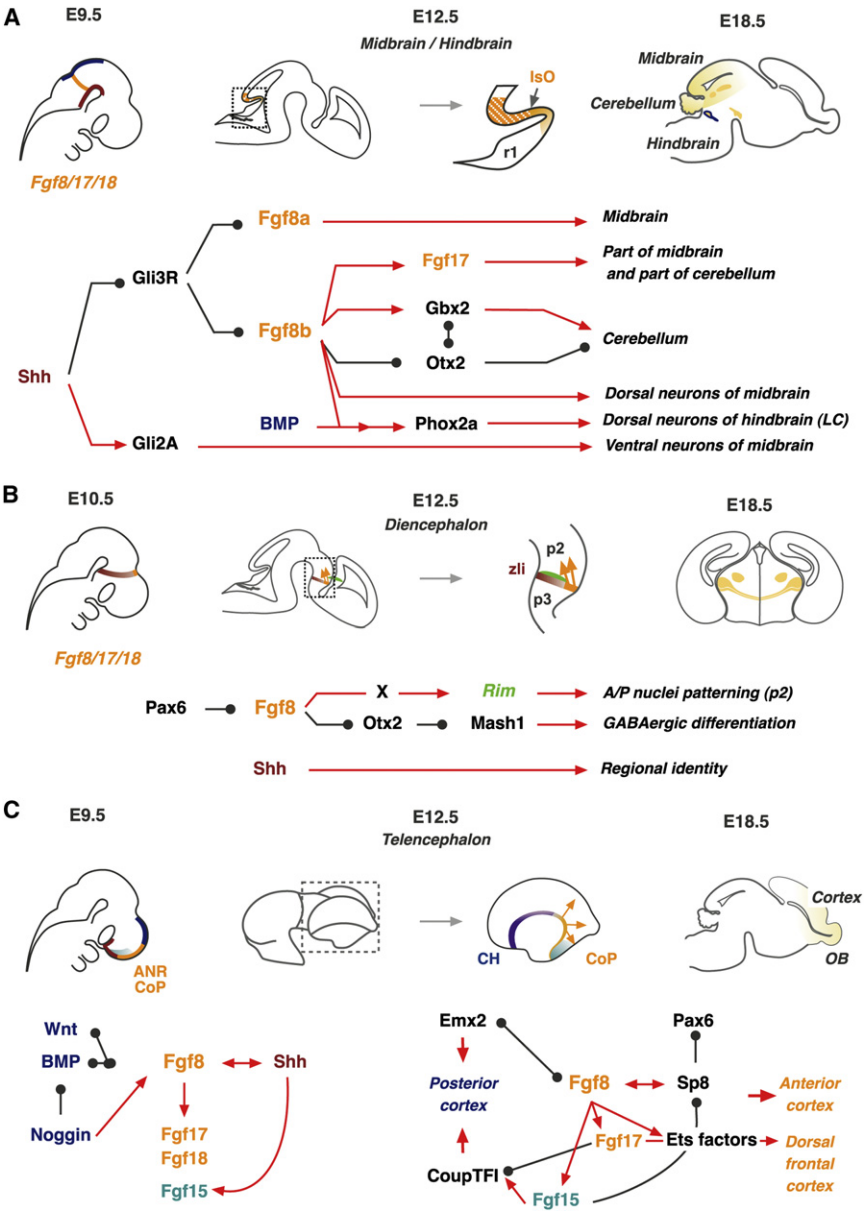


Figure 4. Interactions of FGFs with Other Signaling Molecules in the Developing Brain

FGF8, FGF17, and FGF18 are coexpressed in the signaling center of the isthmic organizer between midbrain and hindbrain (A), the zona limitans intrathalamica of the thalamus (B), and the anterior forebrain (C) from E9.5 to E10.5, with FGF8 playing the major role as it induces the expression of both Fgf17 and Fgf18. By E12.5, FGFs pattern the territories surrounding the signaling centers and begin to specify the identity of neuronal populations, as illustrated at E18.5. FGF signaling (in orange) induces (red arrows) or represses (blue arrows) the expression and/or activity of specific transcription factors and interacts with other signaling pathways, including Shh (purple), Wnt, and Bmp (dark blue). Note that the FGF8 and Shh pathways cooperate in both the mid/hindbrain (A) and the anterior forebrain (C).

(A) Fgf8 expression at the midbrain/hindbrain border between E9.5 and E12.5 spans the isthmic organizer (IsO). Two isoforms of FGF8 have distinct functions, with FGF8a being involved in midbrain patterning and FGF8b in induction of the cerebellum and in specification of dorsal midbrain neurons. As in the telencephalon, FGF17 patterns a smaller territory of the midbrain and cerebellum than FGF8.

(B) In the diencephalon at E10.5, Fgf8 is expressed near the dorsal midline of the p2 domain while Shh is expressed in the zona limitans intrathalamica (zli) at the border between the p2 and p3 domains. At E12.5, FGF8 patterns the anterior part of the p2 domain (presumptive thalamus) (Kataoka and Shimogori, 2008).

(C) In the anterior telencephalon at E9.5, Fgf8 is expressed in the anterior neural ridge (ANR) and commissural plate (CoP) and it patterns the anterior part of the telencephalon, particularly the olfactory bulb (OB) and the anterior cortex. FGF8 interacts with Wnt/Bmp from the cortical hem (CH) and Shh from the ventral neural tube, and induces "anterior" transcription factors (e.g., Sp8, Pax6, Ets) and represses "posterior" factors (Emx2, CoupTF1). FGF17 patterns a subdomain of the anterior cortex, while FGF15 counteracts FGF8/17 activities. The functions of FGF signaling in the ventral telencephalon, e.g., through regulation of Shh and Nkx2.1, are not illustrated.

and Sahara, 2008; Figure 4C). Analysis of mice null mutant for FGF17, which is also secreted by the rostral signaling center, showed that this FGF has a more restricted role in telencephalic patterning and specifically controls the size and position of the dorsal frontal cortex (with important consequences for adult behavior that are discussed later) without affecting the development of the ventral frontal cortex, in contrast with FGF8 which regulates the size of both territories (Cholfin and Rubenstein, 2007, 2008). The divergent activities of FGF17 and FGF8 likely reflect spatio-temporal differences in their expression within the rostral signaling center as well as different affinities for FGFRs. Analysis of mice null mutant for FGF15, a third FGF secreted anteriorly, revealed that this factor has a unique role among telencephalic FGFs as it opposes FGF8 function and suppresses anterior telencephalic fates, at least in part by promoting expression of CoupTF1. Addition of FGF8 and FGF15 to cortical cell cultures differentially activates several kinases acting downstream of FGFRs, suggesting that the two ligands interact with different FGFRs (Borello et al., 2008). In addition to their roles in the specification of areal identities, FGFs also control the differential growth of cortical subdomains, as discussed in the next section.

A combination of experiments, including analysis of FGF8 protein distribution, fate mapping of FGF8-expressing cells, and inhibition of FGF8 signaling with a dominant-negative version of FGFR3c, has demonstrated that FGF8 acts in the telencephalon as a classic morphogen. It forms a diffusion gradient across the entire antero-posterior extent of the telencephalic primordium and acts directly at a distance from its source to impart different positional identities at different

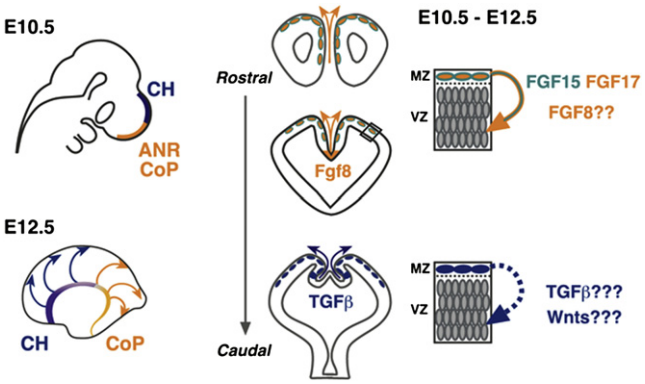


Figure 5. Specification of Cajal-Retzius Cell and Morphogen Spread
At E10.5 in the mouse, the anterior signaling center, also known as anterior neural ridge/commissural plate (ANR/CoP; orange), secretes FGFs while the telencephalic posterior signaling center or cortical hem (CH; blue) secretes Wnts and TGFβs. Together, these molecules pattern the ventricular zone (VZ) of the telencephalon along its anterior-posterior axis (Sur and Rubenstein, 2005). FGF8 and caudal molecules such as TGFβs have been implicated in the specification of distinct population of the pioneer Cajal-Retzius neurons (Hanashima et al., 2007; Siegenthaler and Miller, 2008; Zimmer et al., 2010). In addition, Cajal-Retzius cells generated anteriorly and migrating tangentially in the marginal zone (MZ) have been shown to secrete FGF15 and FGF17 and thus to participate to the spread of morphogens that pattern the telencephalic VZ (Griveau et al., 2010). It is unknown whether Cajal-Retzius cells generated posteriorly in the CH similarly spread Wnt and TGFβ signals while migrating in the MZ.

concentrations (Toyoda et al., 2010). Similarly, secretion of FGFs by the isthmus produces a concentration gradient that generates graded patterns of gene expression in the midbrain (Chen et al., 2009). Direct examination of single molecules of green fluorescent protein (GFP)-tagged FGF8 in living zebrafish embryos showed that FGF8 diffuses in the extracellular space, with its signaling range being controlled by HSPGs and by receptor-mediated endocytosis in receiving cells (Yu et al., 2009).

FGF8 produced anteriorly also induces the development of the telencephalic midline (Okada et al., 2008; Storm et al., 2006) and the generation of particular neuronal populations, including a subset of the pioneer Cajal-Retzius neurons (Zimmer et al., 2010; Figure 5) and gonadotrophin-releasing hormone (GnRH)-producing neurons. This later population deserves special mention, as loss-of-function mutations in either Fgf8 or Fgfr1 in humans produce defects in the specification and the subsequent steps of axon extension and migration of GnRH neurons, resulting in Kallmann syndrome or idiopathic hypogonadotropic hypogonadism, an heterogeneous genetic disorder associated with a deficit of GnRH production (Dodé et al., 2003; Falardeau et al., 2008). The roles of FGFs in axon extension and neuronal migration are discussed below.

Development of Neural Stem Cells

Proliferation

Once neural progenitors have been generated in the developing brain and spinal cord, FGFs play important roles in their survival and expansion (Diez del Corral et al., 2003; Inglis-Broadgate et al., 2005; Maric et al., 2007; Paek et al., 2009; Storm et al., 2006, 2003; Vaccarino et al., 1999). The early expansion of the neural primordium, before neurogenesis begins, involves symmetric divisions of neuroepithelial cells. At the start of neurogenesis, neuroepithelial cells transform into radial glial cells, which divide asymmetrically to generate another radial glia and a postmitotic neuron or an amplifying progenitor (found only in the telencephalon and termed basal progenitor because it divides away from the telencephalic ventricle) (Götz and Huttner, 2005).

Studies of mice mutant for different FGFs have revealed that the FGF family is collectively involved in the progression of neurogenic lineages at each of these steps. FGF2 and FGF8 maintain the proliferative divisions of neuroepithelial cells before the onset of neurogenesis (Raballo et al., 2000; Storm et al., 2006). FGF10 then promotes the maturation of symmetrically dividing neuroepithelial cells into asymmetrically dividing radial glia cells and the initiation of neurogenesis (Sahara and O'Leary, 2009). FGF signaling is required again after neurogenesis has started, to slow down the progression from radial glia to basal progenitors (Kang et al., 2009).

Several of the FGF ligands and receptors that control telencephalic growth are expressed in gradients across the telencephalic vesicles and only regulate the size of limited portions of the cortical primordium. Analysis of mouse embryos carrying hypomorphic or conditional mutations of Fgf8 has established that FGF8, secreted by the rostral signaling center, specifically increases the size of the anterior-ventral telencephalon by stimulating cell proliferation and inhibiting apoptosis (Storm et al., 2006). The study of FGF15 null mutant mice has shown that this factor, which is also secreted anteriorly, opposes FGF8 activity and promotes cell-cycle lengthening and cell-cycle exit in the caudal-ventral cortex, in part by activating the expression of the transcription factor COUP-TF1 (Borello et al., 2008). FGFR3, which is expressed in a gradient with highest levels in the posterior-lateral cortex, has been proposed to control the growth of this part of the cortex by regulating cell-cycle length and duration of the neurogenic phase, based on analysis of mice expressing a constitutively active version of the receptor (Thomson et al., 2009).

Although FGF10 is uniformly expressed throughout the anterior-posterior axis of the cerebral cortex, loss of Fgf10 results in excess cell proliferation only in the anterior cortex, suggesting that other factors with a similar neurogenic activity operate posteriorly (Sahara and O'Leary, 2009). FGF2 has been reported to be expressed across the whole cortical progenitor zone (also known as ventricular zone or VZ) of the cortex, as well as being released by afferent thalamic axons (Dehay et al., 2001), and in contrast to other FGFs it is required throughout the cortex for progenitor divisions during early neurogenesis and the subsequent generation of appropriate numbers of projection neurons (Raballo et al., 2000). Analysis of the adult subventricular zone in mice that are constitutively null mutant for FGF2 or have been infused with the factor suggests that FGF2 might promote progenitor proliferation all the way to adult neurogenesis (Wagner et al., 1999; Zheng et al., 2004). Expression of mutated versions of FGFR1 in adult neural stem cell cultures has implicated the MAPK/Erk pathway in the maintenance of adult stem cell proliferation and the PLCγ/Ca^{2+} pathway in inhibition of astroglial differentiation and maintenance of the neuronal and oligodendroglial differentiation potential of neural stem cells (Ma et al., 2009). However, definitive evidence of a role of

FGF2 in adult neurogenesis (e.g., by adult-brain-specific deletion of the gene) is still lacking, as the null mutation might act only indirectly during embryonic development, by reducing the number of founder cells for adult neural stem cells.

FGF2 is also a potent mitogenic factor for telencephalic progenitors in vitro (Maric et al., 2007), and adding high concentrations of both FGF2 and epidermal growth factor (EGF) has become standard procedure to expand neural stem cells in floating ''neurosphere'' or adherent cultures (Conti et al., 2005; Palmer et al., 1995; Vescovi et al., 1993). In primary cultures of rodent embryonic telencephalon, FGF2 induces responsiveness of neural progenitors to EGF, which might account in part for the synergistic activities of the two factors (Ciccolini and Svendsen, 1998; Lillien and Raphael, 2000). FGF2 promotes the proliferation of neural progenitors in these cultures by shortening the G1 phase of the cell cycle and by inhibiting the generation of postmitotic neurons, via upregulation of cyclin D2 and downregulation of the cyclin-dependent kinase inhibitor p27/kip1 (Lukaszewicz et al., 2002; Maric et al., 2007; Wilcock et al., 2007). Manipulations of FGF signaling in chick embryo explants and zebrafish embryos have shown that FGFs also maintain the progenitor state by opposing the neuronal differentiation activity of retinoid signaling, e.g., through repression of the RA-synthesizing enzyme Raldh2 by FGF8 in the spinal cord and through upregulation of the RA-degrading enzyme Cyp26 by FGF20a in the hindbrain (Diez del Corral et al., 2003; Gonzalez-Quevedo et al., 2010).

Interestingly, functional analysis of several components of the MAPK/Erk pathway, including FRS2α, MEK, Erk2, and C/EBPβ, has revealed a crucial role of the pathway not only in the proliferation but also in the neuronal commitment and differentiation of cortical progenitors (Ménard et al., 2002; Paquin et al., 2005; Samuels et al., 2008; Yamamoto et al., 2005; Figure 2). However, FGFs and FGFRs themselves have not been widely implicated in the restriction of multipotent neural progenitors to the neuronal lineage or their subsequent differentiation, except for the neurogenic function of FGF15 in the telencephalon and midbrain (Borello et al., 2008; Fischer et al., 2011) and a few other instances of FGF signaling promoting cell-cycle exit and neuronal differentiation, e.g., in the retina and cranial placodes (Cai et al., 2010; Lassiter et al., 2009). Whether FGFs or other growth factors acting via the MAPK/Erk pathway, such as PDGF or neurotrophins, are the main inducers of neurogenesis in the cerebral cortex remains an open question.

Gliogenesis

In all vertebrates, neural progenitors generate neurons first and glial cells later, allowing for the establishment of neuronal connections and subsequent addition to the nascent circuits of matching numbers of glial cells. FGF2 induces cortical progenitors to adopt an astroglial fate at the expense of neuronal fates when added to embryonic cortical cell cultures (Morrow et al., 2001; Qian et al., 2000). This finding suggests that FGF2, secreted by cortical neurons, acts on progenitor cells in a negative feedback loop that brings about the switch from neurogenesis to gliogenesis. FGF9, which is also expressed by cortical neurons, might participate in a similar regulatory loop controlling the timing of astrogliogenesis in the cortex (Seuntjens et al., 2009; Figure 6A–6D). FGF promotes astrocyte differentiation in cortical cultures by instigating changes in histone methylation at the promoter of the Glial Fibrillary Acidic Protein (GFAP) gene, which facilitates activation of the promoter by other gliogenic pathways such as the CNTF-Jak-STAT pathway (Song and Ghosh, 2004). FGF signaling has also been implicated in the specification of the other major glial cell type, oligodendrocytes. Oligodendrocytes are generated in successive waves by progenitors located at different dorso-ventral positions in the neural tube, including ventral progenitors that are specified by Shh and dorsal progenitors that are induced by a Shh-independent process. Manipulations of FGF signaling in mouse, chick, and zebrafish, both in vitro and in vivo, support a role of the pathway in the generation of Shh-independent dorsal oligodendrocyte progenitors via induction of the oligodendrocyte determinant Olig2 and the oligodendrocyte and astrocyte determinant Sox9 (Chandran et al., 2003; Esain et al., 2010; Gabay et al., 2003; Kessaris et al., 2004; Naruse et al., 2006). Interestingly, the role of FGF signaling in gliogenesis is conserved in *Drosophila*, where two FGF8-like ligands, expressed in either glial cells or neurons and signaling through different FGFR downstream pathways, promote the proliferation and migration of glial cells, and their differentiation and subsequent wrapping of axonal processes, respectively (Franzdóttir et al., 2009).

Neuronal Circuit Assembly

Neuronal Migration

Migration of newborn neurons is an essential step in the morphogenesis of the vertebrate brain and in the formation of neural circuits. FGF signaling has a prominent role in the migration of a variety of cell types in the embryo, including neurons. FGF18 is secreted by neurons of the cerebral cortex and it signals back to cortical progenitors, as shown by the FGF18-dependent expression of the Ets transcription factors Pea3, Erm, and Er81 by VZ cells (Hasegawa et al., 2004; Figures 6E–6G). Blocking FGF signaling or the activity of Ets proteins by expressing dominant-negative constructs in the cortical VZ leads to neuronal migration defects, suggesting that FGF18 mediates a feedback loop through which neurons that have reached their final position control the migratory behavior and laminar position of the next wave of neurons (Hasegawa et al., 2004) (Figures 6E–6G). FGFs, signaling through FGFR1 and FGFR2, also promote the translocation of astroglial cells from the VZ to the surface of the cortex (Smith et al., 2006). In particular, FGFR1 is required for the migration of astrocytes at the dorsal midline, where they form a structure (the glial sling) that allows commissural axons to cross to the contralateral hemisphere. Fgfr1 mutant mice lack brain commissures, including the corpus callosum and the hippocampal commissure, and homozygous mutations of the Fgfr1 gene in humans result in Kallman syndrome with a similar agenesis of the corpus callosum (Dodé et al., 2003; Smith et al., 2006; Tole et al., 2006). The *Drosophila* FGFR breathless is also involved in midline glial cell migration and formation of commissures in the *Drosophila* embryo (Klämbt et al., 1992). In the cerebellum, FGF9 secreted by granule neurons signals through FGFR1 and FGFR2 induces Bergmann glial cells to adopt a radial morphology that provides a substrate for granule neuron migration (Lin et al., 2009). FGFs are therefore involved in multiple feedback mechanisms through which neurons control

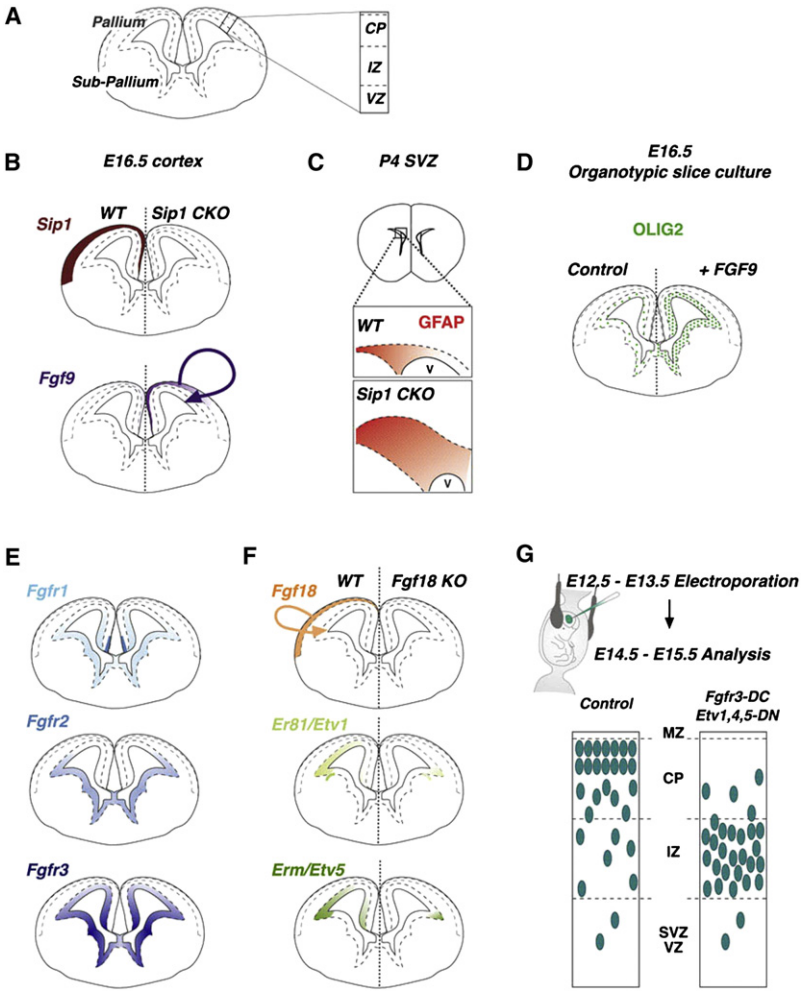


Figure 6. FGFs in Feedback Loops between Cortical Neurons and Progenitors

(A) Subdivisions of the embryonic telencephalon: cortical plate (CP); intermediate zone (IZ); ventricular zone (VZ).

(B and C) Mice mutant for the transcription factor Sip1 present a premature expression of Fgf9 by CP neurons (B) and an increase and precocious generation of glial progenitors (not shown), followed by an enhanced postnatal astrogliogenesis marked by upregulation of the astrocytic marker GFAP (Seuntjens et al., 2009) (C).

(D) FGF9 induces expression of the oligodendroglial progenitor marker Olig2 in organotypic slice cultures of embryonic cerebral cortex, suggesting that it participates in a positive feedback loop whereby CP neurons promote the specification of VZ progenitors to a glial fate (Seuntjens et al., 2009).

(E) The expression domains of the FGF receptors FGFR1, 2, and 3 in the telencephalon at E12.5–E13.5 overlap with distinct gradients.

(F) FGF18 is expressed by mature neurons in the CP and analysis of *Fgf18* mutant mice showed that it induces the expression of the Ets transcription factors Er81/Etv1, Pea3/Etv4, and Erm/Etv5 in progenitors of the VZ (Hasegawa et al., 2004).

(G) Overexpression of dominant-negative forms of Ets factors or of FGFR3 in mouse embryonic telencephalon resulted in migration defects of cortical neurons, suggesting that FGF18 and Ets proteins participate in a positive feedback loop between CP neurons and VZ progenitors that promotes the migration of newborn cortical neurons (Hasegawa et al., 2004).

the specification, migration, and differentiation of precursor cells in the cerebral cortex and cerebellum.

Axon Pathfinding

Another important step in the assembly of neural circuits, the directional growth of axons toward their targets, also requires FGF signaling. FGFs act as target-derived signals that control the growth, navigation, branching, and target recognition of axons in multiple brain regions. In particular, FGFs emanating from signaling centers are in strategic positions to coordinate axon navigation with other aspects of brain organization. Grafts of FGF8-soaked beads in embryonic brains or brain explants have provided evidence that FGF8 produced by the isthmus acts as a chemoattractant for axons forming the trochlear nerve in the anterior hindbrain, while it indirectly repels axons from midbrain dopaminergic neurons by inducing expression of the chemorepellent Sema3F in the midbrain (Irving et al., 2002; Yamauchi et al., 2009). Analysis of Fgf8 hypomorphic mutant mice showed that FGF8 similarly controls the formation of axonal projections between cortical areas in the telencephalon (Huffman et al., 2004). FGF signals produced outside the nervous system also guide embryonic motor axons to their targets. The transcription factor LHX3 induces expression of Fgfr1 by a particular class of spinal motor neurons, resulting in attraction of their axons to FGF-producing somites (Shirasaki et al., 2006). In addition to their guidance role, FGFs also have strong axon outgrowth and branching activities. FGF2 promotes interstitial branching of cortical pyramidal axons in culture by enhancing the pausing and enlargement of their growth cones, suggesting that it contributes to the formation of collateral axon branches during innervation of the cerebral cortex (Szebenyi et al., 2001). Interestingly, other molecules than FGFs may promote axon growth by interacting with FGFRs, as reported for cell adhesion molecules (CAMs) in both *Drosophila* and mammalian neuronal cultures (García-Alonso et al., 2000; Saffell et al., 1997). Interactions of FGF signaling pathways with other signaling mechanisms have not yet been extensively examined, and they have the potential to greatly contribute to the diversity and complexity of FGF functions in axon pathfinding and other steps of neural development.

Synapse Specification

Once axons have reached their targets, synapses are generated by the coordinated assembly of presynaptic and postsynaptic structures. FGF22 and the closely related family members FGF7 and FGF10 are expressed by neurons during the period when they receive synapses, and they promote synaptogenesis in chick motoneuron cultures by inducing synaptic vesicle aggregation in axon terminals (Umemori et al., 2004). Remarkably, analysis of synapse formation in the hippocampus of Fgf22 and Fgf7 mutant mice has shown that FGF22 is specifically required for presynaptic differentiation at glutamatergic (excitatory) synapses while FGF7 has a similar role at GABAergic

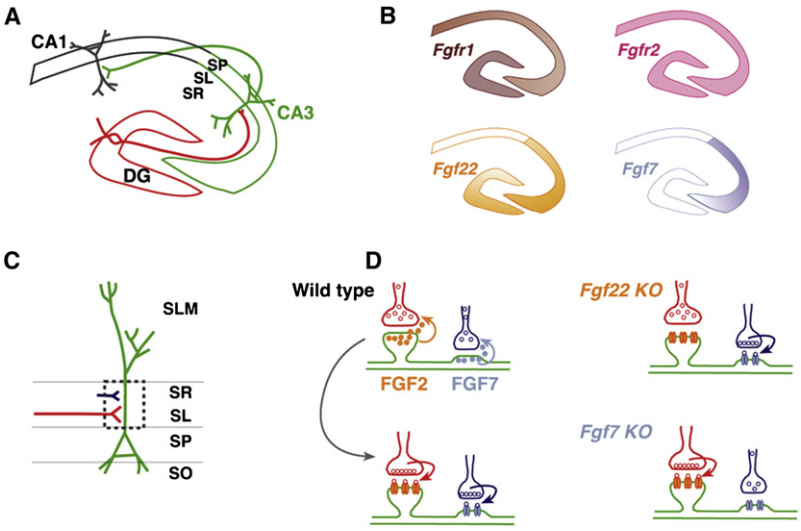


Figure 7. FGFs Regulate Synaptogenesis
(A and C) Pyramidal neurons from the CA3 region of the hippocampus receive excitatory inputs from the dentate gyrus (DG) and local inhibitory inputs that form synapses in the stratum radiatum (SR) and stratum lucidum (SL).
(B) Expression patterns of Fgf7 and Fgf22 and their cognate receptors Fgfr1 and Fgfr2 in the hippocampus.
(D) FGF22 and FGF7 are both present in dendrites of hippocampal pyramidal neurons but are differentially distributed in excitatory (red) and inhibitory (blue) synapses, respectively (Terauchi et al., 2010). Both FGFs act as presynaptic organizers but FGF22 promotes the organization of glutamatergic VGLUT1+ excitatory synapses while FGF7 organizes inhibitory VGAT+ GABAergic synapses. As a result, the differentiation of excitatory or inhibitory nerve terminals on dendrites of CA3 pyramidal neurons is specifically impaired in mutants lacking Fgf22 or Fgf7, respectively (Terauchi et al., 2010).

(inhibitory) synapses (Terauchi et al., 2010; Figure 7). Transfection of GFP-tagged molecules into cultured hippocampal neurons showed that FGF22 and FGF7 are specifically targeted to glutamatergic and GABAergic synapses, respectively. Moreover, exogenous applications of FGF22 or FGF7 cluster glutamatergic and GABAergic vesicles to different extents, suggesting that the specificity of the two factors lies not only in their localization to different dendritic subdomains on the postsynaptic side but also in the activation of different signaling pathways on the presynaptic side (Terauchi et al., 2010). Indeed FGF22 has been shown to interact in vitro with both FGFR1b and FGFR2b while FGF7 only interacts with FGFR2b, suggesting that these FGFs control the specificity of presynaptic nerve terminal-postsynaptic target recognition in part through differential binding to FGFR isoforms.

FGFs in Disease

Neurological Diseases

Not surprisingly given their widespread involvement in neural development, FGFs have been associated with multiple neurological disorders. Postmortem studies have shown that several FGF ligands and receptors are downregulated in the prefrontal cortex and hippocampus of patients with major depression, suggesting that dysregulation of FGF signaling is involved in the disease, e.g., by contributing to the atrophy of the hippocampus and prefrontal cortex reported in depressed patients (Evans et al., 2004; Riva et al., 2005). A role of FGFs in the action of antidepressants has also been proposed, based on the findings that treating patients and rodents with specific serotonin reuptake inhibitors increases Fgf expression levels in the prefrontal cortex and other brain regions, and that acute or chronic administration of FGF2 reduces anxiety and depression-like behaviors in rats (Evans et al., 2004; Perez et al., 2009; Turner et al., 2008). FGF2 could contribute to the action of antidepressants by reversing hippocampal and cortical atrophy as well as through its mitogenic effect on hippocampal progenitors, since some of the behavioral effects of antidepressants require the stimulation of neurogenesis in the adult hippocampus (Duman and Monteggia, 2006; Perez et al., 2009; Zhao et al., 2007). Dysregulation of FGF signaling during development has also been proposed to increase vulnerability to neuropsychiatric disorders such as autism spectrum disorder (ASD) (Rubenstein, 2010; Vaccarino et al., 2009). According to this hypothesis, mutations in autism susceptibility candidate genes might interfere with FGF signaling and produce defects in brain growth and cortical circuit formation that predispose affected individuals to the disease. This hypothesis has received some support from animal studies, in particular in Fgf17 mutant mice where patterning defects of the frontal cortex during development result in specific deficits in social behaviors and working memory in adults (Scearce-Levie et al., 2008).

Besides neuropsychiatric disorders and Kallman syndrome (see above), FGF signaling deficiencies have been implicated in neurodegenerative diseases, including a progressive spinocerebellar ataxia (Laezza et al., 2007; van Swieten et al., 2003) and Parkinson's disease (PD). A genetic association between single-nucleotide polymorphisms in the Fgf20 gene and increased risk of PD has been identified in several large family studies and has been confirmed in some but not all subsequent studies (Clarimon et al., 2005; van der Walt et al., 2004; Wang et al., 2008). Fgf20 is specifically expressed in the substantia nigra of the midbrain and the cerebellum, where it promotes survival of substantia nigra dopaminergic neurons, the neurons most affected in PD (Murase and McKay, 2006). Carriers of one of the Fgf20 polymorphisms also present diminished verbal episodic memory and a significantly enlarged hippocampal volume, suggesting that genetic variations in Fgf20 also modulate brain structure and function in healthy subjects (Lemaitre et al., 2010).

Neuronal Repair

Lesions to the adult nervous system reactivate developmental processes such as the proliferation and differentiation of progenitors present at the site of injury. Members of the FGF family, in particular FGF2, are strongly involved in neuroprotection and repair in response to neural tissue damage. Expression of Fgf2 and Fgfr1 is upregulated in glial cells and neural stem cells after neuronal damage, and analysis of mice mutant for Fgf2 or

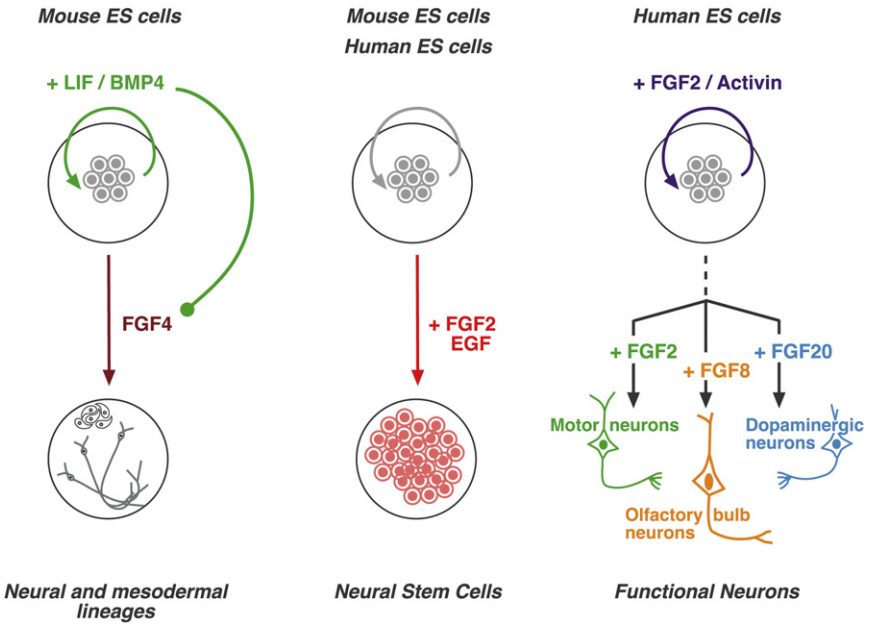


Figure 8. FGFs and the In Vitro Generation of Neurons

FGFs are involved in three distinct steps of the in vitro generation of neurons from embryonic stem (ES) cells. First, FGF4 produced endogenously by ES cells promotes the specification of mouse ES cells along the neuronal and mesodermal lineages. Leukemia inhibiting factor (LIF) blocks FGF4 activity and maintain ES cells in a self-renewing and undifferentiated state (left panel). Second, FGF2 increases the efficiency of generation of multipotent and self-renewing neural stem (NS) cells from ES cells and in combination with epidermal growth factor (EGF), it promotes the rapid expansion of NS cells in adherent or "neurosphere" cultures (center panel). Third, different FGFs have been used to guide the differentiation of human ES cells toward different neuronal subtypes, as described in the text (right panel).

Fgfr1 has shown that both genes are required for neuronal regeneration following epileptic episodes, transient ischemia, or traumatic brain injury (Fagel et al., 2009; Yoshimura et al., 2001). Exogenous FGF2, alone or in combination with other factors such as brain-derived neurotrophic factor (BDNF) or EGF, also promotes significant neuronal regeneration following neuronal loss induced by epilepsy or ischemia or in genetic models of neurodegenerative diseases such as Huntington's disease (HD) (Jin et al., 2005; Nakatomi et al., 2002). FGF2 appears to enhance the proliferation and differentiation of endogenous progenitor cells present in the dentate gyrus (e.g., in mice with hippocampal lesions) and in the subventricular zone (in HD mice) as well as outside these neurogenic regions. Exogenous or endogenous FGF2 also has a role in protection against neuronal death, notably in mouse models of neurodegenerative diseases such as HD or PD (Jin et al., 2005; Timmer et al., 2007).

Generating Neurons in a Dish

The mammalian nervous system has, however, a limited capacity for self-repair. Efforts are being made to circumvent this limitation and boost the repair process by transplanting exogenous cells into sites of injury. FGFs can be used to generate, expand, and differentiate neurons in vitro and therefore have a major role to play in such cell replacement therapies (Figure 8).

Pluripotent mouse embryonic stem (ES) cells self-renew indefinitely in culture when exposed to the cytokine leukemia inhibitory factor (LIF), but they can differentiate into neurons under the influence of endogenous FGF. ES cells produce FGF4, which, if left unchecked, acts in an autocrine/paracrine manner to block self-renewal and promote commitment to the mesodermal or neural lineages. BMP and BMP signaling inhibitors can then act downstream of FGF signaling to promote nonneural and neural fates, respectively (Kunath et al., 2007; Stavridis et al., 2007). In self-renewing ES cell cultures, LIF/Stat3 signaling inhibits lineage commitment by blocking the FGF4 signaling pathway downstream of Erk (Kunath et al., 2007; Figure 8).

Exposure to exogenous FGF2, even in the absence of BMP antagonists, greatly improves the efficiency with which mouse and human ES cell cultures commit to a neural fate and generate neural precursors (Ying et al., 2003; Zhang et al., 2001). FGF2 converts these cells into neural stem cells characterized by rapid self-renewing and the potential to generate neurons, astrocytes, and oligodendrocytes (Figure 8). This acquired tripotent neural stem cell state, which does not exist in vivo, results from the induction by FGF2 of multiple genes, including EGFR and Olig2, which provide high proliferative capacity and glial differentiation potential to the treated cells (Gabay et al., 2003; Hack et al., 2004; Laywell et al., 2000; Palmer et al., 1999; Pollard et al., 2008; Zhang et al., 2001). When transplanted into neonatal mouse brains or lesioned adult mouse brains, FGF2-induced progenitors can integrate into brain tissue and differentiate into neurons and astrocytes (Rosser et al., 2000; Zhang et al., 2001). However, their repair capacity in animal models with acute brain injuries or slowly progressing neurodegenerative conditions is rather limited. A more promising approach is to first differentiate these cells in culture and transplant them afterwards (Rosser et al., 2007). Protocols are thus being developed to differentiate neural progenitors into medically relevant cell types and FGFs, which are implicated in the development of multiple neuronal lineages in the embryo, again have an important role to play in this step. For example, FGF2, FGF8, and FGF20 have been used to guide the differentiation of in vitro expanded human neural stem cells toward spinal motor neurons, olfactory bulb projection neurons, and midbrain dopaminergic neurons, respectively (Correia et al., 2008; Eiraku et al., 2008; Grothe et al., 2004; Jordan et al., 2009). Looking to the future, there is no doubt that further deepening our understanding of the functions of FGFs in neural development will benefit the quest for effective treatments of neurological diseases.

Conclusion

This review has surveyed the remarkable functional diversity of FGFs in the developing nervous system. A striking illustration

of this diversity is provided by the vast range of cellular processes regulated by isthmic FGFs, including cell survival, proliferation, specification of cell identity, neuronal differentiation, and axon growth (Partanen, 2007; see above). Multiple mechanisms contribute to the functional diversity of the FGF signaling system. Foremost is the vast number of FGF ligands, which elicit diverse biological responses because of their different affinities for FGF receptors and HSPGs (Figure 1). The multiple isoforms of the four FGFRs and the highly complex family of HSPGs, which are integral components of the FGF ligand-receptor complex, also have the potential to hugely diversify signaling activities downstream of FGFs. The activation of FGF receptor complexes can trigger several signal transduction cascades (Figure 2), and crosstalk with other pathways, such as the synergistic and antagonistic interactions with Wnts, EGF, retinoic acid, and Notch through which FGFs regulate progenitor divisions (Ciccolini and Svendsen, 1998; Diez del Corral et al., 2003; Gonzalez-Quevedo et al., 2010; Israsena et al., 2004; Yoon et al., 2004), further expands the range of cellular responses to FGFs. In addition to this multiplicity of signaling mechanisms, the response of neural tissues to the same FGF signal can also vary across space and time. For example, different domains of the neural plate adopt distinct fates when exposed to FGF8. This differential response is controlled by spatially restricted transcription factors, including the homeodomain factor Six3, which instructs FGF8-induced neural plate cells to adopt a forebrain fate, and the homeodomain protein Irx3, which directs cells exposed to the same signal to adopt a midbrain fate (Kobayashi et al., 2002). Such competence factors are likely to play an important role in the diversification of FGF functions, and elucidating how they modulate the cellular response to FGF signaling is an exciting direction for future research.

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